Quantification and data optimisation of heart and brain studies in conventional nuclear medicine

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6. Summary and future directions.

Part I deals with cardiac studies.

In chapter 2, methods aimed at evaluating left ventricular ejection fraction are described.

In the first part, the performance capacities and limitations of a single crystal digital gamma camera are evaluated with respect to the high count rate required for an accurate measurement of ejection fraction by first pass radionuclide angiography. Using the ultrashort half-lived $^{191}Ir^{m}$, the high yield of the generator (120 mCi - 4400 MBq) provided more than 1 million real counts per second whereas the measured camera saturation was 420 kcps. Compared to a large field of view detector system, a small field of view (20 cm) has the advantage to have less activity in the field of view reducing the non-linearity problem. Using an ^{191}Os reference source, we were able to correct for the non-linearity up to 320kcps.
Applied to patient studies, a maximum count rate of 250 kcps was measured during the left ventricular phase, with a system resolution loss of 2-3 mm in fast mode. Repeated LVEF determination at 2 min-intervals in 50 patients was highly reproducible with a mean difference of 2.08$\pm$1.55 EF units (r=0.97). Furthermore, the simultaneous use of $^{191}Ir^{m}$ and of ^{201}Tl permitted a combined evaluation of myocardial perfusion and function both at rest and during exercise.

In the second part, the performances of different software for left ventricular ejection fraction (LVEF) and volume measurements by gated myocardial tomography are studied, and the influence of modifying acquisition and reconstruction parameters are evaluated, especially in patients with small hearts.
In patients with a normal-sized heart, the different commercially available software for quantitative gated SPET was well correlated. Changes in matrix size had little influence on LVEF and volumes whereas smoothing significantly modified the volume measurements. In small-sized hearts on the other hand, LVEF at the higher range were frequently observed. The results of quantitative gated SPET were software, matrix size and smoothing dependent. Probably more realistic, significantly lower LVEF and larger volumes were found by increasing the matrix size or sharpening the filter.

Chapter 3 deals with the quantification of perfusion and metabolism in the specific context of myocardial viability assessment.

The first part reports the development and clinical validation of a quantification whereby the activity of the myocardial perfusion tracer ^{99m}Tc -sestamibi and the free fatty acid metabolism tracer ^{123}I-BMIPP was quantified on a pixel-to-pixel basis. Based upon the difference in uptake between sestamibi and BMIPP, the presence and extent of normal, viable and scar myocardium was expressed in % of the surface of the left ventricle as a whole and of the three main coronary arteries separately and visually displayed using colour-coded polar maps. This analysis was applied to patient studies. Inter-observer difference in the % viable myocardial surface was rather small, amounting to 1.5% at most. Moreover, a good concordance was found between the presence of decreased sestamibi and BMIPP uptake and a significant stenosis on coronary angiogram.

In the second part the influence of high-energy emitting photons on the spectrum of iodine-123 was quantified for low- and medium-energy collimators in phantom studies.

In the third part this scatter influence was shown in patient studies. The newly developed quantification with colour-coded polar maps was applied to calculate the extent of viable tissue, defined as a mismatched uptake with BMIPP uptake lower than sestamibi. Since the contribution of scatter in the iodine images is not negligible, its potential influence on the calculated amount of viable tissue was measured by quantifying sestamibi and BMIPP uptake without correction, after background subtraction, and with scatter correction. Echocardiographically assessed changes in segmental wall motion at six months after treatment was used as the gold standard. The evolution of contractile function was correctly predicted in 64% of the segments without correction, 79% after background subtraction and 93% after scatter correction.

The fourth part contains the abstracts of the articles that we have published about the clinical applications of myocardial perfusion/metabolism imaging in patients with chronic ischemic heart disease post-infarction. From these clinical studies, it seems that ^{99m}Tc -sestamibi alone is a suboptimal tracer to identify myocardial viability in patients with chronic ischemic heart disease post-infarction, even when a quantitative analysis is applied. Adding a metabolic tracer such as ^{123}I-BMIPP significantly improves the diagnostic accuracy, and the combination of sestamibi and BMIPP imaging is able to identify myocardial viability in chronic ischemic heart disease with an accuracy similar to that reported in the literature for ^{18}F-FDG PET, or for the combined BMIPP/sestamibi study in the acute or subacute phase of a myocardial infarction. However, due to the influence of high energy photons in the iodine-123 imaging, scatter correction is recommended and special attention must be paid to the used collimator.

Part 2 deals with brain studies.

In Chapter 4, an absolute quantification method of the brain perfusion is described.

Methodologically, because of the clinical need for an absolute SPECT parameter, a simple approach was developed using calibrated point sources as scaling factor, to display tomographic images as regional ^{99m}Tc HMPAO brain uptake (rBU) per cm^3 brain tissue in percent of the injected lipophilic dose. The method was validated on Jaszczak and Hoffman phantoms using a three detector SPECT system with parallel and fan-beam collimators. A mean reproducibility of 7.2 % was obtained in human studies. Application of the method in 33 healthy volunteers pointed to body surface as the most important factor explaining interindividual variability when compared to brain volume. The same study stressed the need in longitudinal studies for normalization of rBU to the rest heart rate and suggested the absence of significant influence of minor stress on regional ^{99m}Tc HMPAO brain uptake.
The former evaluation of cerebellar rBU in a healthy population was extended to patients suffering from dementia of the Alzheimer type (DAT). rBU values in operator-defined cerebellar regions of interest may be considered highly symmetrical, reproducible and stable in time in healthy volunteers. Moreover, after cumulative corrections for body surface and brain volume a similar and reproducible, absolute cerebellar ^{99m}Tc HMPAO uptake value was found for the group of DAT patients and the group of healthy volunteers. The presented findings suggested that the cerebellum may be a good choice as reference region in SPECT analysis of DAT patients.

In Chapter 5, dopamine transporters in the striatum are quantified.

Parkinson's disease is characterised by a severe degeneration of dopaminergic neurons in the substantia nigra, resulting in a loss of dopamine transporters in the caudate and putamen nuclei visualized with ^{123}I-FP-CIT. Using SPECT, it is well know that semi-quantitative analysis of small organs like the striatum is hampered by the partial volume effect due to the low spatial resolution of the gamma camera. For source diameters < 12 mm, the count density was reduced by a factor 3 to 5.
We devised a resolution independent method by calculating the total striatum activity divided by the mean brain activity per ml using two very large region of interests. Knowing that the volume of the human striatum is about 20 ml and the real concentration of dopaminergic system radioligands is 8 to 9 times higher in the striatum than in the remaining brain tissue**,** the total striatal to the mean brain activity/cm^3 values between 150 and 200 obtained in our normal subjects seem consistent. Moreover using classical striatal and occipital ROIs, we obtained an inter-observer variability of 11.4 % compared to 3.1% using the resolution independent method.
Additionally the total striatal uptake was expressed as percentage of injected dose using a gamma camera calibration factor. Globally, good separation was obtained between normal and Parkinsons using both, the conventional and our method. When corrected for the patient's weight, striatal uptake expressed in percentage of the injected dose allowed a better separation between normal subjects and Parkinson's patients compared to the conventional method.
For more accurate anatomic localization of defects, we created two images for visual interpretation: a striatum/brain ratio image and an uptake image expressing the % of the injected dose per ml striatal tissue.
The resolution independent method is gamma-camera, acquisition and reconstruction independent. Using this method, results from different centres can directly be compared without the need of any special soft- or hardware adjustment.

Future directions.

The current trends in conventional nuclear instrumentation and data analysis can be divided in three main topics: image fusion, software development and new devices.
The fusion of modalities becomes standard in clinical practice. Hybrid imaging systems SPECT equipment with X-ray tubes (CT) are on the market. Initial attempts to co-register functional and anatomical images acquired on two different machines failed to disclose the proper alignment and are too cumbersome on a routine basis (1). SPECT/CT improves the diagnostic accuracy of SPECT in various clinical situations (2) although misalignment artefacts between emission and transmission can still be present, especially in cardiac studies (3). A debate is still going on pro and contra attenuation correction for cardiac studies (4). However a CT based attenuation map improves semi-quantitative cardiac studies (5,6) and precise absolute quantification becomes realistic when including also scatter and collimator depth corrections in the iterative reconstruction methods (7,8). Attempts are also made to correct partial volume effect in small textures by anatomical information (9).
Improvement of reconstruction algorithm's remained a major topic on the IEEE meeting in Rome 2004. New software starts entering clinical practice. Three dimensional models of coronary artery tree created by biplane angiograms are aligned with 3D perfusion SPECT images (10). Motion-frozen gated images can be created using phase-to-phase motion vectors (11). Statistic parametric mapping (SPM), frequently used for brain research becomes a standard procedure (12).

The major improvement in nuclear medicine is expected from new devices and material. The goal is to reduce the intrinsic spatial resolution and energy resolution (13,14). New detection materials with better physical characteristics than NaI concerning stopping power, energy resolution, light output, fragility and density will most likely replace NaI crystals (15). Position sensitive photo multiplier tubes (PSPMT) has become available which are coupled to pixellated NaI(Tl) crystals or new scintillation material like CsI(Tl) (16,17). It is expected that new imaging devices with several thousands of tiny crystals or semiconductor array detectors will improve the sensitivity and specificity of clinical studies (15,18). Increased detector sensitivity will permit dynamic tomographic studies and more precise quantitative data for compartimental analysis already performed for planar studies. Small surgical probes based on CZT semiconductors or PSPMT tubes become popular in surgery tracing regional metastases (19). It remains however questionable whether these small devices, now a day used for animal studies or as surgical probes, can be developed as large detectors for human studies at a reasonable price.

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